REMARKS

Claims 45 to 55 are pending in the application. Claim 55 has been withdrawn from consideration in view of the Examiner's restriction requirement. Because the eight compounds listed in claim 55 are entirely within the scope of claims 45 and 46 and exactly the same as the compounds listed in claims 47, 49 and 52, all of which have already been examined, if any of claims 45 to 54 are found allowable, applicants respectfully request rejoinder of claim 55.

Claims 45, 46, 50, 51 53, and 54 are finally rejected under 35 U.S.C. 103(a). Applicants request reconsideration and withdrawal of the rejection for the reasons set forth herein.

The rejection of claims 47, 48, 49 and 52 has been withdrawn. However, no further comment on the state of these claims can be found in the Office Action. Are these claims allowed? There is a box (Box number 5) on the PTOL-326 Office Action Summary Form which accompanied this action that should indicate allowed claims, if any. This box has not been checked and no claims are indicated as being allowed. The PTOL Form also fails to indicate anything about these claims. Are they rejected, objected to, considered by the Examiner to be withdrawn? Clarification is respectfully requested.

I. The Rejection of Claims 45, 46, 50, 51, 53 and 54 under 35 U.S.C. 103(a).

In the opinion of the Examiner, applicant's prior argument amounted to the position that the cited art was not relevant "because the references do not teach the identical disorder of the instant claims". Applicants do not appreciate this overly simplified mischaracterization of their argument.

Ajito teaches benzimidazole compounds as having platelet aggregation **inhibitory** activity. This is the exact **opposite** of applicant's activity of **enhancing** platelet activity.

Applicants argument is that Ajito **teaches away** from their discovery, that their particular benzimidazole compounds increase platelet activity. The skilled worker trying to make compounds that increase platelet activity would find the teaching in Ajito to lead away from the use of benzimidazole compounds because Ajito teaches that benzimidazole compounds inhibit platelet activity.

Teaching away is a well established element of unobviousness. When a cited reference is relied on as a "teaching away" from the claimed invention, it is inappropriate for the Examiner to simply side step the argument by mischaracterizing this evidence of unobviousness as simply "not teaching the identical disorder of the instant claims". The Examiner is obligated to address applicant's argument and explain why one skilled in the art would take the teaching of Ajito that indicates benzimidazole compounds have platelet **inhibitory** activity as a motivation to: 1) modify Ajito's compounds in the way necessary to prepare applicant's specific compounds; 2) in anticipation of achieving platelet **enhancing** activity. Such rational is absent from the Examiner's Action. Absent such rational, the Examiner has failed to establish a prima facie case of obviousness.

Moreover, the Examiner states that the methods of Ajito are "closely related" to the method of the instant claim. Such generalized statements without any additional reasoning fail to assist in the determination of obviousness. Applicant's invention relates to TPO receptor agonist compounds that increase platelet count and increase platelet activity. The compounds of Ajito are άvβ3 antagonist that inhibit platelet activity. Applicants submit that it defies logic and reasoning to conclude that the methods of Ajito and the methods disclosed in the instant application are "closely related". Applicants respectfully request that the Examiner state for the record how the methods of Ajito are "closely related" to the methods of the instant application or withdraw the rejection.

Regarding Ayal-hershkovitz, applicants previously pointed out to the Examiner that Ayal-hershkovitz is directed to heparanase inhibitor compounds useful in the treatment of cancer, inflammatory disorders and autoimmune disorders. Further, nowhere in Ayal-hershkovitz is there motivation modify the compounds disclosed therein in the manner needed to arrive at applicants compounds. And no such motivation is alleged in either of the Examiner's Office Actions. Moreover, Ayal-hershkovitz recites over 100 preferred disease states for use with their compounds and indicates that the list is not limited only to the preferred disease states. Applicants again submit that Ayal-hershkovitz fails to motivate the skilled worker to modify the compounds therein to arrive at applicants claimed compounds in anticipation that those compounds would be TPO receptor agonist useful in increasing platelet production. The Examiner's response was an over simplified statement "a reference is good for all that it teaches". Again, what is missing here is the analysis. Surely, a reference is not patentably destroying for all that it recites. In the statement above, what does the Examiner mean by "good"? "Good" for what? How does the Examiner interpret the term "teaches"? Does a reference "teach" merely because a word is found on a page therein or does it "teach" only what the skilled reader would deduce form the data provided therein and does not 'teach" what the skilled worker would realize is only conjecture?

Applicants submit obviousness is a complicated subject requiring sophisticated analysis. Instead of analyzing the references, identifying the differences and supplying the motivation needed to build a prima facie case of obviousness, the Examiner merely recites "a reference is good for all that it teaches". Section 103 requires more.

Raeymaekers is directed to yet a third class of benzimidazole compounds for use in treating androgen dependent disorders. Applicant's again note the absence of a structural

analysis as to why one skilled in the art would be motivated to modify Raeymaekers to arrive at the presently claimed compounds.

Furthermore, the Examiner states that Raeymaekers teaches compounds useful for treating disorders relating to androgens, the compound Danazol is cited as a modified androgen useful for treating thrombocytopenic conditions and the conclusion is somehow drawn that Raeymaekers teaches compounds to treat thrombocytopenia!? Other than applicants, the person most surprised by this analysis would be Raeymaekers. From even a casual reading of Raeymaekers it is overtly obvious that the inventors never intended or believed that their compounds would ever be thought of as treating thrombocytopenic conditions, except perhaps by the instant Examiner. The Examiner's statement that Raeymaekers teaches compounds useful for "treating disorders relating to androgens" is overly general and misleading. Why did the Examiner use the open-ended phrase "treating thrombocytopenic conditions" when the compounds of Raeymaekers are clearly anti-androgens? The compounds of Raeymaekers treat androgen dependent disorders (See title of the invention). When you treat androgen dependent disorders (that is disorders that result form androgens) you need to **reduce** the androgens. Raeymaekers discloses small molecule benzimidazole compounds that reduce the biosynthesis of androgenic hormones, thereby inhibiting the formation of androgens and treating disease states that result of excess androgens. In view of this disclosure, the Examiner somehow finds reason for the skilled worker to administer a modified androgen (Danazol) to treat thrombocytopenic conditions. The Examiner then somehow concludes that the skilled worker would find it obvious to modify Raeymaekers benzimidazole compounds to applicant's different benzimidazole compounds in anticipation of achieving applicant's unity, instead of Raeymaekers utility.

The skill worker looking to prepare compounds that increase platelet production and platelet activity would read Raeymaekers to disclose benzimidazole as lowering androgen

levels and find no motivation to work in the area. Applicants also cite Raeymaekers as a teaching away in that the benzimidazole compounds therein are disclosed a anti-androgens and one skilled in the art trying to prepare compounds that increase platelet count and increase platelet activity would be lead away form benzimidazole compounds as they are disclosed as having anti-androgen activity.

In view of the obvious disclosure of anti-androgen activity in Raeymaekers as evidenced by the title of the invention and clearly disclosed utility in the specification, applicants conclude that by characterizing Raeymaekers as teaching "treating disorders relating to androgens" the Examiner is turning a blind eye to the clear teaching in Raeymaekers in order maintain a rejection where motivation is needed to increase androgen levels. Applicants believe such misguided six-degrees-of-separation rejections will never be an acceptable criterion for rejection under section 103 and will be overturned on appeal.

Moreover, applicants request that the Examiner indicate how the compound Danazol is pertinent to the instant rejection. Where did this compound come from, one of the cited references?

The facts of the matter here are that applicants discovered specified novel benzimidazole compounds that are agonist of the TPO receptor and result in increased platelet count and increased platelet activity. The Examiner has twice rejected the claims without any compound analysis as to why one skilled in the art would be motivated to specifically modify the different classes of benzimidazole compounds in the cited references to what applicants have done in their invention. There is merely the Examiner's conclusion that applicant's compounds and the compounds of the cited references all relate to benzimidazole compounds so they are

all obvious over each other. Such is not a proper analysis under section 103. Further, the Examiner ignored applicant's arguments that Ajito and Raeymaekers teach away form their claimed invention and that "benzimidazole" compounds is an extremely broad classification of compounds with many varied pharmaceutical activities associated with the different classes of benzimidazole compounds which do not lead to applicant's compounds or applicants utility. Applicants contend that the Examiner has failed to make out a prima facie case that applicant's specific compound modifications to arrive at their specific utility were obvious. In reply the Examiner forgoes analysis and recites generalities such as "closely related", "a reference is good for all it teaches" and "well within the technical grasp of one of ordinary skill in the art". The Examiner's argument is tantamount to citing several references that teach benzimidazole compounds as having various pharmaceutical activities and concluding that all subsequently discovered benzimidazole compounds that have pharmaceutical activity are thereby rendered obvious. Such generic one size fits all rejection for benzimidazole inventions is not a proper analysis under section 103 and must be withdrawn.

In order to keep applicant's previous remarks in the current record the arguments for patentability over the cited references submitted in their previous response are repeated below for the currently rejected claims.

Claims 45, 46, 50, 51 53, and 54 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over *Ajito et al.* (WO 99/38849, US 6,451,800), in view of *Ayal-hershkovitz et al.* (WO 02/060374) and *Raeymaekers et al.* (US 4,859,684) because, in the opinion of the Examiner, both Ajito et al. and Ayal-hershkovitz et al. teach the treatment of thrombocytopenia using benzimidazole compounds and "reasonably suggest" the same use of benzimidazole compounds such as those taught by Raeymaekers et al. because the compounds belong to the same art recognized class.

Applicants contend that "reasonably suggest" is not the proper standard for obviousness under section 103. An invention is obvious if one of ordinary skill in the art would consider it logical to anticipate with a high degree of probability that a trial of it would be successful. *In re Pantzer et al.* 144 USPQ 415.

Applicants newly discovered compounds are agonist of the TPO receptor. Upon agonizing the TPO receptor the target cells produce platelets. The resultant increase in platelet count treats disease states wherein low platelet count is an indication, or thrombocytopenia.

The Examiner cites Ajito et al. as teaching benzimidazole compounds in the treatment of thrombocytopenia. This is simply not the case. In fact Ajito et al. teaches the exact opposite. The benzimidazole compounds of Ajito et al. are indicated as having άvβ3 antagonist, GP IIb/IIIa antagonist and/or platelet aggregation **inhibitory** activity. The compounds of Ajito et al. are blood thinners. They hinder or prevent platelet activity so that clots or platelet thrombosis do not form or are broken up. The compounds of Ajito et al. are given to people who want to decrease platelet activity. Applicant's compounds are given to people who have low platelet count, people who want to increase platelet activity.

The Examiner cites *Ayal-hershkovitz et al.* as teaching benzimidazole compounds in the treatment of thrombocytopenia. The compounds of *Ayal-hershkovitz et al.* are indicated as heparanase inhibitors and useful in the treatment of cancer, inflammatory disorders and autoimmune disorders. The vast majority of this application is dedicated to the position that the heparanase inhibiting compounds disclosed therein have anti-proliferative activity, such as anticancer, inflammatory and in the treatment of autoimmune disorders. However, page 28 of *Ayal-hershkovitz et al.* does indicate a myriad additional disease states for the disclosed

compounds, one of which is thrombocytopenia. The skilled worker would find no reason to believe the compounds of *Ayal-hershkovitz et al.* would be useful in enhancing proliferation from the disclosure or data in the specification. And no reason to believe that the compounds of *Ayal-hershkovitz et al.* would be useful in increasing platelet count.

Notwithstanding, the Examiner premises the rejection on the belief the all benzimidazole compounds belong to the same art recognized class, that both *Ayal-hershkovitz et al.* and Ajito et al. disclose benzimidazole compounds for use in treating thrombocytopenia, and thus the art reasonably suggest the benzimidazole compounds of Raeymaekers et al. are useful in the treatment of thrombocytopenia. Applicants cite *Ayal-hershkovitz et al.* and Ajito et al. for the premise that the pharmaceutical activity of benzimidazole compounds is a highly unpredictable art. The benzimidazole compounds of Ajito et al. decrease platelet activity while the benzimidazole compounds of *Ayal-hershkovitz et al.*, according to the Examiner, increase platelet activity. There is no disclosure in either of these references alone or in combination with *Raeymaekers et al.* that teaches or suggests how to alter the substituents on benzimidazole compounds in order to control which activity the compounds will exhibit. Further, there is no guidance in *Ayal-hershkovitz et al.* and/or Ajito et al. that would tell the skilled worker whether to expect platelet increasing activity or platelet decreasing activity, or heparanase inhibitory activity and/or άvβ3 antagonist activity and/or GP IIb/IIIa antagonist activity and/or TPO agonist activity by making the substituent changes on a benzimidazole ring that applicants have discovered in their current invention.

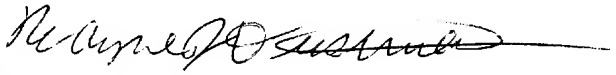
Ayal-hershkovitz et al., Ajito et al. and *Raeymaekers et al.*, alone or in combination with Raeymaekers et al., fail to provide the requisite motivation or desirability to prepare applicant's novel benzimidazole compounds with a high degree of probability of obtaining TPO agonist

compounds that are useful in the treatment of thrombocytopenia. Absent the requisite motivation or desirability to prepare applicant's benzimidazole compounds the rejection here must be withdrawn.

Applicants submit that the references cited by the Examiner, alone or in combination, do not render their invention prima facie obvious and request that the rejection be withdrawn.

Applicants therefore submit that all reasons for rejection have been addressed and that the pending claims are allowable. Applicants respectfully request rejoinder of claims 55 and a Notice of Allowance. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned attorney at the number indicated below.

Respectfully submitted,



Wayne J. Dustman
Attorney for Applicant
Registration No. 33,870

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-5023
Facsimile (610)270-5090
n:\wjd\TPO\P51399\response to final OA dated 5-20-2008.doc